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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.  
P.O. BOX 2938  
MINNEAPOLIS, MN 55402

[REDACTED] EXAMINER

BERCH, MARK L

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25

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application N .</b>	<b>Applicant(s)</b>
	09/313,048	CARSON ET AL.
	<b>Examiner</b>	<b>Art Unit</b>
	Mark L. Berch	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 16 October 2000.

2a) This action is FINAL.                    2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-11,13-15,18 and 19 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-11,13-15,18 and 19 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
 If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
 a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>21</u>	6) <input type="checkbox"/> Other: _____

## DETAILED ACTION

### *Continued Prosecution Application*

The request filed on 10/16/2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/313048 is acceptable and a CPA has been established. The delay is regretted. An action on the CPA follows.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 13-15, 18, 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Choice a) for Z is not possible. An alkyl cannot comprise a double bond, O or N atoms. Alkyl is a group of the formula  $-C_nH_{2n+1}$ , as such it cannot be unsaturated or have heteroatoms. If applicants intend that the carbon atoms be substituted by e.g. O, or interrupted by O, or whatever, then the claim language must be adjusted accordingly.

2. The "ester of an amino acid" at the fourth from last line of claim 1 is not possible. An ester is a molecule, e.g. ethyl carbamates, and thus cannot be a moiety as the claim requires.

3. The term “C<sub>6</sub>-C<sub>10</sub> heteroaryl” in claim 1 contradicts what the specification states. The sentence starting at page 4 line 4 says that these have 5-6 ring atoms, at least one of which must be O, X or N, meaning that the ring can have at most 5 carbons, not 6-10.
4. Similarly, claim 6 is improperly dependent on claim 1, since the pyridyl has only 5 carbons, not 6 as required.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear which disorders this covers. There are some inflammatory disorders in which proinflammatory cytokines are not the primary mediators, but in which the role of proinflammatory cytokines has not been investigated, so it is not known if they fall within claim 11. Note that claim 11 requires only an association, which could cover as little as an incidental triggering of the production of a single proinflammatory cytokine.

Claims 11-15, 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The broadening of original claim 11 clearly constitutes new matter. Page 4, lines 1-3 clearly conveys that these compounds inhibit the release of  $\alpha$ -TNF, and not proinflammatory cytokines in general such as IL-1. Page 4 says that as a result of the inhibition of this release, treatment of a certain category of

disorders is possible, not as the result of any proinflammatory cytokine. Further, the examiner notes that the specification's language is hedged. The phrase "can be useful" only presents a possibility. The phrase "can be useful" is not the same as "is useful".

Claims 11 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Because of the broad scope of he linker A, the terminal group Z, and the substituents R2 and X, billions of compounds are covered.

(b) Scope of the diseases covered. Claim 11 covers many, if not most, and quite possibly all inflammatory diseases. It covers even diseases where the proinflammatory

cytokines are not the primary mediators. For example, Immune Complex (IC)-induced inflammatory responses (e.g. IgG Immune complex-Induced Lung or Skin Injury), which not primarily based on proinflammatory cytokines (these come primarily from either the soluble proteins of the complement system or the cellular receptors for IgG, the Fc receptors), do to some extent trigger the cytokine cascade, including e.g. IL-6. This would then meet the claim 11 limitation of "associated with", since there is an association.

The scope of treating inflammation generally, or almost generally, is extraordinarily broad. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. It is one of the most pervasive of all body processes. Inflammation is a very general term which encompasses a huge variety of specific processes.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Mechanistically, chronic

inflammation encompasses a broad spectrum of immunologic processes, including antibody formation, antibody-dependent cell-mediated cytotoxicity, and cell-mediated immunity (delayed-type hypersensitivity). Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Cholecystitis is gallbladder inflammation usually caused by a gallstone that cannot pass through the cystic duct. In those cases, it normally cannot be treated by pharmaceuticals but instead the gallbladder is removed. Cholecystitis without the formation of gallstones, called acalculous cholecystitis, is caused by bacteria such as *Salmonella*, *Staphylococcus*, *Streptococcus* (as part of scarlet fever), and leptospirosis, and thus may be treatable by treating the underlying infectious agent. Acute

inflammation of the gall bladder can also arise from typhoid; treatment is with antibiotics.

In gout, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Acute attacks of gout are treated with colchicine (to inhibit of MSU-induced chemotactic factor release by PMNs) and after the acute phase with allopurinol to control the blood levels of uric acid.

Pseudogout, sometimes referred to as calcium pyrophosphate disease (CPPD), is inflammation caused by calcium pyrophosphate (CPP) crystals. It is treated with nonsteroidal anti-inflammatory drugs , corticosteroids and Colchicine.

Sinusitis is the inflammation of the mucosal lining of one or more of the 4 cavities near the nasal passages (ethmoid, maxillary, frontal, and sphenoid sinuses). It commonly accompanies upper respiratory viral infections which obstruct the opening, but such obstruction can also arise from abnormalities in the structure of the nose, enlarged adenoids, diving/swimming, infections from a tooth, trauma to the nose, and foreign objects that are stuck in the nose. Bacteria, notably Streptococcus pneumonia, Haemophilus influenza, and Moraxella catarrhalis grown in the trapped secretions. In most cases it requires no treatment, but antibiotics may be given, along with acetaminophen for pain and nosedrops, for relief of symptoms.

Pharyngitis is infection and inflammation of the throat (including the nasopharynx, uvula, and soft palate)and tonsillitis is of the tonsils. These are caused by a variety of viruses (adenoviruses, influenza viruses, parainfluenza viruses, Epstein-Barr virus, enteroviruses, Herpes simplex virus), mycoplasmas (e.g. Mycoplasma pneumoniae), and bacteria (Group A Beta Hemolytic Streptococci (GABHS),

**Streptococcus pyogenes, Neisseria Gonorrhea, Hemophilus Influenza Type B) as well as fungal infections, parasitic infections, cigarette smoke, and unknown causes.**

**Similarly, Osteomyelitis is the inflammation of bones, generally caused by bacteria (most commonly Staphylococcus Aureus). The disease can be caused by fungi or viruses. Dacryoadenitis, an inflammation of the tear gland, can arise from infectious mononucleosis, mumps, gonorrhea, or influenza. Conjunctivitis (pink eye) is inflammation of the conjunctiva and can be caused by many microorganisms, including staphylococci, Haemophilus influenzae, streptococci, gonococci, and viruses such as adenoviruses. Treatment in all of these cases, when possible, is thus to the underlying infectious agent.**

**Rheumatoid arthritis is an inflammatory bone disease causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-1, IL-18, TNF- $\alpha$  and IFN- $\gamma$ .**

**Pneumonia is an inflammation of the lungs. Lobar pneumonia affects one or more sections (lobes) of the lungs. Bronchial pneumonia (or bronchopneumonia) affects patches throughout both lungs. Bacterial pneumonia is caused by various bacteria notably Streptococcus pneumoniae. Viral pneumonia is caused by viruses (such as respiratory syncytial, parainfluenza, and influenza), Other causes are fungi, mycoplasmas, rickettsias (especially Q fever), Chlamydia, or parasites. It can also occur as a hypersensitivity, or allergic response, to agents such as mold, humidifiers, and animal excreta, and in such a case would be treated with anti-allergic agents. Treatment may include antibiotics for bacterial pneumonia. Antibiotics may also speed recovery**

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from mycoplasma pneumonia and some special cases. There is no clearly effective treatment for viral pneumonia.

**Adult (or Acute) Respiratory Distress Syndrome (ARDS)** is severe inflammation in both lungs resulting in an inability of the lungs to function properly. ARDS is a devastating, often fatal, inflammatory lung condition that usually occurs in conjunction with catastrophic medical conditions, such as pneumonia, shock, sepsis, and trauma. No specific therapies currently exist for ARDS patients. Treatment primarily involves supportive care in an intensive care unit , including use of a mechanical ventilator and supplemental oxygen to help patients breathe.

Chronic bronchitis is a long-term inflammation of the bronchi, which results in increased production of mucus, as well as other changes. Chronic bronchitis has no specific organism recognized as the cause of the disease. Cigarette smoking is cited as the most common contributor to chronic bronchitis, followed by bacterial or viral infections and environmental pollution. Treatment may include bronchodilators for inhaled medications, oxygen supplementation, lung reduction surgery and lung transplantation.

Acute bronchitis is the inflammation of mucous membranes of the bronchial tubes and is usually caused by infectious agents such as bacteria or viruses. It may also be caused by physical or chemical agents -- dusts, allergens, strong fumes -- and those from chemical cleaning compounds, or tobacco smoke. (Acute asthmatic bronchitis may happen as the result of an asthma attack, or it may be the cause of an asthma attack.)  
Acute bronchitis is usually a mild, and self-limiting condition, with complete healing and

return to function. Most of the treatment is supportive of the symptoms, and may include analgesics, such as acetaminophen for fever and discomfort.

Asthma is a chronic, inflammatory lung disease involving recurrent breathing problems. It is characterized by three airway problems: obstruction, inflammation, and hyper-responsiveness. These lead to contraction of airway muscles, mucus production, and swelling in the airways. There are many different asthma triggers.

Myocarditis is an inflammation of the muscular middle layer of the heart (myocardium) Viruses, bacteria, and noninfectious diseases can cause it. Treatment is primarily supportive e.g. drugs may be used to improve the heart's ability to contract and to remove extra fluids from the body. Unless the underlying infectious agent itself is treatable, this inflammation is not itself treated.

Glossitis is inflammation of the tongue. Local causes of glossitis include bacterial or viral infection, mechanical irritation or injury from burns, rough edges of teeth or dental and oral appliances, or other trauma; exposure to irritants (tobacco, alcohol, hot foods, or spices), and sensitization (to e.g. toothpaste, mouthwash, breath fresheners, dyes in candy, plastic in dentures or retainers) anemia and other B vitamin deficiencies, erythema multiform, pemphigus vulgaris, syphilis, and other disorders. It can be inherited. Corticosteroids such as prednisone may be given to reduce the inflammation. Antibiotics, antifungal medications, or other antimicrobials may be prescribed if the cause of glossitis is an infection. Anemia and nutritional deficiencies must be treated, often by dietary changes or other supplements.

Meningitis is the inflammation of the meninges—the surrounding 3-layered membranes of the brain and spinal cord, and the fluid it is bathed in, (CSF). It can be

caused by virtually any known infectious agent. Thus, if it is caused by *Haemophilus influenzae* or *Neisseria meningitis*, the antibiotic derivative rifampin would be used.

**Myelitis** is inflammation of the spinal cord.

**Dactylitis** is an inflammatory affection of the fingers.

**Inclusion body myositis** is an inflammatory slowly progressive proximal myopathy which may cause dysphagia and mild to moderate muscle wasting.

Steroids and immunosuppression have generally been generally ineffective. Its pathogenesis is unknown, but ubiquitin, prion protein, and tau protein has been found in these inclusions.

**Encephalitis** is inflammation of the brain itself, often caused by a group of arboviruses. Treatment of encephalitis is largely supportive because no specific antiviral agents, except for that which works against herpes simplex virus, are available for therapy.

Inflammation in the brain is an significant component of some important neurodegenerative conditions, including Alzheimer's Disease, AIDS dementia, Pick's Disease, Parkinson's Disease, and Huntington's Disease. The circumstances here are poorly understood because while there does not appear to be lympho-infiltrative processes, there is neuropathological evidence for immune activation. Thus, inflammation may be a disease-aggravating or even a disease-ameliorating factor in pathogenesis, or a non-contributory consequence of the injurious cascade of neurodegeneration and thus incidental.

Hepatitis is an inflammation of the liver, usually caused by viral invasion, notably hepatitis A, B and C, but sometimes Epstein-Barr virus; herpes simplex viruses; measles, mumps, and chicken pox viruses; and cytomegaloviruses. Treatment, when possible, is with antivirals. Inflammation of the liver also take the form of alcoholic hepatitis.

Lupoid hepatitis is an autoimmune disorder.

Hemorrhoids is an enlarged or varicose condition of the hemorrhoidal veins and tissues around the anus, either internal or external. Anything which obstructs the free circulation of the blood in the portal system will give rise to hemorrhoids. Constipation, straining at stool, diarrhea, dysentery, rough toilet paper, uncleanliness, pelvic tumors, displacement of the uterus and pregnancy are among the most common causes.

There is a series of inflammatory problems directly connected to neutrophil-endothelial cell adhesion (NECA). These include frostbite injury, bacterial meningitis, acute airway inflammation, allograft rejection, hemorrhagic shock, septic shock, ischemia and reperfusion injuries.

Urethritis is an inflammation of the duct that leads from the bladder to the body's exterior. It is often due to fecal contamination or irritation due to physical or chemical substances (e.g. introduction of foreign bodies into the urethra, bubble bath, or soap) or gonorrhea. Treatment may simply involve the withdrawal of the offending chemical agent, or the administration of antibiotics, when *Neisseria gonorrhoeae* is involved.

Inflammation can arise from the eruption of teeth in a child (teething).

Inflammation of the nails can arise from chronic paronychia, fungus (especially *Candida albicans*), trauma, impaired circulation, and dermatitis.

Bright's disease (or glomerulonephritis) is inflammation of the glomeruli and the nephrons, the structures in the kidney that produce urine. It usually results from an infection, such as a streptococcal infection, that occurs somewhere else in the body. There is no real treatment beyond relief of the symptoms.

Thyroiditis is an inflammation of the thyroid gland, and takes three forms. Hashimoto's Thyroiditis (chronic lymphocytic thyroiditis) is the most common type of thyroiditis. It is an autoimmune disorder, and treatment is to start thyroid hormone replacement. For De Quervain's Thyroiditis (subacute or granulomatous thyroiditis), treatment is usually bed rest and aspirin to reduce inflammation. Occasionally cortisone and thyroid hormone may be used. Silent Thyroiditis usually arises following pregnancy. Treatment is usually bed rest with beta blockers.

Regional enteritis (Crohn's disease or ileitis) is an autoimmune disorder which is associated with the presence of *Mycobacterium paratuberculosis*. It can affect any part of the gastrointestinal tract but most commonly affects the ileum. The inflammation is controlled primarily by regulation of diet, antibiotics if abscesses and fistulas are present, sometimes Prednisone and other corticosteroids, and surgery.

Another category of inflammatory disorders is Interstitial lung disease, or ILD, (interstitial pulmonary fibrosis), a term that includes more than 180 chronic lung disorders, which may be chronic, nonmalignant (non-cancerous) and noninfectious. Interstitial lung diseases are named after the tissue between the air sacs of the lungs called the interstitium -- the tissue affected by fibrosis (scarring). The common link between the many forms of ILD is that they all begin with an inflammation. The three main kinds are bronchiolitis - inflammation that involves the bronchioles (small

airways); alveolitis - inflammation that involves the alveoli (air sacs); and vasculitis - inflammation that involves the small blood vessels (capillaries). More than 80 percent of interstitial lung diseases are diagnosed as pneumoconiosis, a drug-induced disease, or hypersensitivity pneumonitis. Some other types are idiopathic pulmonary fibrosis, bronchiolitis obliterans, histiocytosis X, chronic eosinophilic pneumonia, granulomatous vasculitis, Goodpasture's syndrome and pulmonary alveolar proteinosis. The cause of interstitial lung disease is not known, however, a major contributing factor is thought to be inhaling environmental pollutants. Other contributing factors include Sarcoidosis, certain drugs, radiation, connective tissue or collagen diseases and family history. Treatments may include corticosteroids, influenza or pneumococcal pneumonia vaccine but these are of limited effectiveness.

Many Occupational Lung Diseases are inflammatory in origin, arising from repeated and long-term exposure to certain irritants on the job. These include for example asbestosis, coal worker's pneumoconiosis (caused by inhaling coal dust), silicosis (caused by inhaling free crystalline silica), byssinosis (caused by dust from hemp, flax, and cotton processing, also known as brown lung disease), aluminosis, anthracosis ("collier's lung", from the accumulation of carbon from inhaled smoke or coal dust in the lungs), chalcosis (stone-cutters' lung disease, due to inhaling stone dust), siderosis (occurring in iron workers, produced by the inhalation of particles of iron), tabacosis, hypersensitivity pneumonitis (caused by the inhalation of fungus spores from moldy hay, bird droppings, and other organic dusts and occupational asthma (caused by inhaling certain irritants in the workplace, such as dusts, gases, fumes, and vapors).

Pulmonary Sarcoidosis causes small lumps, or granulomas, which generally heal and disappear on their own. However, for those granulomas that do not heal, the tissue can remain inflamed and become scarred, or fibrotic. Pulmonary sarcoidosis can develop into pulmonary fibrosis. Bronchiectasis, a lung disease in which pockets form in the air tubes of the lung and become sites for infection, can also occur. Treatment may include the use of corticosteroids.

Stomatitis, inflammation of the mouth, and mucositis, inflammation of the mucosa can arise from sources as diverse as *Candida albicans*, dentures, chemotherapy and radiation therapy to the head, neck or mouth ("Radiation mucositis"). It may be secondary to infection, trauma, systemic diseases or autoimmune mechanisms. These come in many forms, such as aphthous ulcers, Acute Necrotizing Ulcerative Gingivitis i.e. "trench mouth", and Lichen Planus. Herpetiform ulcers treatment has ranged from antibiotics, immunosuppressants and yogurt, to *Lactobacillus* capsules, tetracycline and systemic steroids. Palliative measures include topical anesthetics, Vitamin E, analgesics, and coating agents. Antiviral agents may be used if viral origin is established.

Rhinitis is a reaction that occurs in the eyes, nose and throat when airborne irritants (allergens) trigger the release of histamine. Histamine causes inflammation and fluid production in the fragile linings of nasal passages, sinuses, and eyelids. The two categories of rhinitis are allergic rhinitis (seasonal and perennial) and nonallergic Rhinitis (including eosinophilic, rhinitis medicamentosa, vasomotor Rhinitis, neutrophilic rhinosinusitis, and others), which come from fumes, odors, temperature or atmospheric changes, smoke, etc. Treatments for nonallergic rhinitis include oral medications, inhaled medications, immunotherapy, and surgery for some conditions.

Wegener's Granulomatosis is a disease that usually begins as a localized granulomatous inflammation of upper or lower respiratory tract mucosa and may progress into generalized necrotizing granulomatous vasculitis and glomerulonephritis. The cause is unknown. Although the disease resembles an infectious process, no causative agent has been isolated. Treatment is with immunosuppressive cytotoxic drugs.

Pancreatitis is inflammation of the pancreas and can arise from abdominal trauma, or the formation of gallstones that obstruct the common bile duct. It can be associated with excessive ingestion of alcohol; with disorders such as cystic fibrosis or Reye's syndrome; or with scorpion stings. Infectious causes include mycoplasmas, Epstein-Barr viruses, Coxsackie viruses, leptospirosis, hepatitis viruses, mumps, congenital German measles, Ascaris worms, and syphilis. The inflammation per se is generally not treatable. Treatment is usually supportive and consists of the management of pain and intravenous feeding.

Neuroretinitis is a type of inflammation of the retina and optic nerve of the eye ("optic neuritis"). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis, toxocara, Sarcoidosis and cat-scratch disease. Treatment is thus to the underlying cause. For example, Diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in the retina or in the subretinal space. Anthelmintic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine. Vogt-Koyanagi-Harada syndrome (Harada's disease) is an acute

inflammatory, immune-mediated disorder that can cause choroidal neovascularization, severe chorioretinal atrophy, and secondary glaucoma.

River blindness arises from inflammation of the eye caused by larvae (microfilaria) of the nematode *Onchocerca volvulus*, although the *Wolbachia* bacteria may be involved as well.

Other eye inflammations include scleritis and episcleritis, inflammation of tissues on the sclera; choroiditis, inflammation of the middle coat (choroid) of the eyeball, and uveitis, which is inflammation of the parts of the eyes that make up the iris.

Gastritis is inflammation to the stomach lining. Atrophic gastritis is characterized by the loss of the stomach cells that are responsible for manufacturing acid, pepsin, and intrinsic factor. This condition occurs in older people or those suffering from *Helicobacter pylori*. Erosive (hemorrhagic) gastritis occurs when shallow ulcers or sores develop on the upper layer of the stomach lining, usually because of the excessive ingestion of a stomach irritant such as aspirin or alcohol.

There can also be mentioned appendicitis, which can occur when a hard piece of stool blocks the opening of the appendix, causing swelling and inflammation.

The great majority of skin problems involve some type of inflammation, such as response to physical injury (e.g. sunburn, ticks, abrasion, or a bee sting), acute allergic contact dermatitis (such as poison ivy), and infections (such as boils and cold sores). Ingrowing hairs, or pili incarnati, can cause acute pustular reactions. Cancerous lesions of the skin frequently show some degree of inflammatory response. Acne's inflammation is caused by leakage of sebum and keratin debris outside the distended pilosebaceous duct. The bacillus *Propionibacterium acnes*, which populates the lesions,

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may also contribute indirectly to this inflammation by metabolizing the sebum to produce irritant fatty acids. Inflammation in skin problems is usually the result of the release of chemical mediators in the skin, notably histamine, peptides (kinins) and fatty acids (prostaglandins and leukotrienes), which are formed enzymatically in response to e.g. injury. Medications designed to counteract inflammation in the skin may or may not antagonize the effects of the particular type of mediator involved, if that is known. The inflammation can take many different forms, including redness, (from dilation of blood vessels); heat, (from increased blood flow); swelling (from leakage of fluid from the small blood vessels); whealing reactions (hives, nettle rash, urticaria) in which vascular changes predominate, and pain or itching. Blisters (from enzymes released from inflammatory cells, resident cells of the skin, or blood plasma components) can cause the breakdown of proteins responsible for the structural integrity of the skin, leading to serious inflammatory disorders such as pemphigus. In addition, the affected skin may feel indurated (hardened) because of the deposition of the coagulation protein fibrin and the infiltration by inflammatory blood cells (lymphocytes, histiocytes, and polymorphonuclear leukocytes).

Prostatitis, inflammation of the prostate, comes in several different forms, including those of bacterial origins, and those which are not, including chronic abacterial prostatitis and asymptomatic inflammatory prostatitis. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases.

Cystic fibrosis (CF) is an inherited disease characterized by an abnormality in the glands that produce sweat and mucus. It is chronic, progressive, and is usually fatal.

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The basis for the problem with CF lies in an abnormal gene, which results in an atypical electrolyte transport system within the cells of the body. The abnormal transport system causes the cells in the respiratory system, especially the lungs, to absorb too much sodium and water. This causes the normal thin secretions in our lungs to become very thick and hard to remove. The high risk of infection in the respiratory system leads to damage in the lungs, lung that do not work properly, and eventually death of the cells in the lungs. The most common causes for infection in the lungs are *Staphylococcus aureus*, *Haemophilus influenza* and *Pseudomonas aeruginosa* (PA). The disorder itself is largely untreatable.

Osgood-Schlatter disease is a common form of inflammation of the knee in active adolescents. It has not pharmaceutical treatment per se. Other inflammations of the knee include Sinding-Larsen-Johansson disease, Patellofemoral syndrome, and osteochondritis dissecans.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation.

Claim 13 is limited to autoimmune diseases. Again, this is a very broad category, as these can arise from several diverse mechanisms, all of which can result in inflammation. There are four basic mechanisms underlying autoimmune disease: 1.

Antibody mediated diseases: a specific antibody exists targeted against a particular antigen (protein), which leads to its destruction and signs of the disease. An example is myasthenia gravis where the target is the acetylcholine receptor in the neuromuscular junction. 2. Immune-complex-mediated diseases: antibodies are produced against proteins in the body. These combine into large molecules that circulate around the

body. In systemic lupus erythematosus (SLE) antibodies are formed against several components in the cell's nucleus (hence the anti-nuclear antibody test (ANA) for SLE). Most notably antibodies are made against the body's double stranded DNA, and form circulating soluble complexes of DNA and antibody, which break down in skin causing an increased sensitivity to ultraviolet light and a variety of signs. As the blood is filtered through the kidneys, the complexes are trapped in the glomeruli and blood vessels, causing the kidney to leak protein - glomerulonephritis. They also cause leakage in other blood vessels, and there may be hemorrhaging, as well as accumulating in synovial fluid and causing signs of arthritis and joint pain. Rheumatoid arthritis results from immune complexes (IgM class antibody called rheumatoid factor) against part of the patient's own immune system (part of its IgG molecules). These form complexes that are deposited in the synovia of the joint spaces causing an inflammatory response, joint swelling, and pain. The collagen and cartilage of the joint breaks down and is eventually replaced by fibrin which fuses the joints - ankylosis.

3. Antibody and T Cell-mediated diseases: T cells are one of two types (the other being B-cells), which mediate immune reactions. Upon exposure to a particular antigen, they become programmed to search for and destroy that particular protein in future. Once a patient has been exposed to an antigen, he will be able to mount a much faster response to it the next time it encounters it. Thyroiditis (autoimmune hypothyroidism) seems to be of mixed etiology. Several target antigens have been identified, including thyroglobulin the major hormone made by the thyroid.

4. Diseases arising from a deficiency in complement:

When an antigen and antibody react they may activate a series of serum enzymes (the

complement system) whose end result is either the lysis (breakup) of the antigen molecule or to make it easier for phagocytic cells like the macrophages to destroy it.

Known autoimmune disorders include multiple sclerosis, autoimmune uveitis, rheumatoid arthritis, Addison's disease, thyroiditis, atrophic gastritis, myasthenia gravis, idiopathic thrombocytopenic purpura, hemolytic anemia, systemic lupus erythematosus, primary biliary cirrhosis, Wegener's granulomatosis, polyarteritisnodosa, erythema nodosum leprosum, autoimmune uveitis, Guillain-Barré syndrome (GBS), allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell anemia, polychondritis, scleroderma, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, type I diabetes, autoimmune optic neuritis, uveitis posterior, or interstitial lung fibrosis, alopecia, Sjogren's Syndrome, Goodpasture Syndrome, Myasthenia Gravis, inflammatory bowel disease and many more.

(2) The nature of the invention and predictability in the art: The invention is directed toward the treatment of disease and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage information provided on page 16 is completely generic; that is, it's the same information regardless of disease.

(4) State of the Prior Art: The prior art has established that there is no common mechanism by which all, or even most, inflammations arise. Examples of pro-inflammatory cytokines include IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, IL-18, MIP-1 $\alpha$ , IFN- $\gamma$  and TNF- $\alpha$ . The prior art knows that mediation of inflammation is among the most pervasive and complex of all body process. The Reference Benjamin K. Gill, "Diagram Representing the Roles of Cytokines in Inflammatory Responses" <http://attila.stevens-tech.edu/chembio/bgill/IL10K.html> downloaded from the Internet 8/12/02 shows the complex interactions among just the cytokines, and just in certain types of inflammatory responses.

Further, the prior art knows that there are many paradoxical features in the inflammation system. As an example, in lung inflammation, nitric oxide appears to be a pro-inflammatory mediator in acute situations e.g. ARDS but anti-inflammatory in more stable situations. As a second example, the cytokine TGF-beta-1 possesses both pro-inflammatory and anti-inflammatory activities. Virtually all cells have TGF-beta-1 receptors, and the cytokine has many other roles other than in inflammation.

Thus, the prior art knows that, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

(5) Working Examples: There are no working examples of treatment of any actual disorder at all. There is one example for "adjuvant arthritis", a somewhat artificial disease in rats.

(6) Skill of those in the art: For a compound or genus to be effective against inflammation generally is contrary to the present understanding of medical science. It

establishes that it is not reasonable to any agent to be able to treat inflammation generally. That is, the skill is so low that no compound effective generally against inflammatory disorders has ever been found. In terms of the individual inflammatory disorders, this is completely varied. It ranges from areas where the skill level is high, as in asthma, to ARDS, where the skill level is so low that there is no effective pharmacological treatment.

(7) The quantity of experimentation needed: Owing to the factors listed above, especially in points 1(a), 1(b), 4 and (6), experimentation needed will be extensive. Because of the sheer scope of this claim language, dozens of unrelated diseases will have to be tested. Many of these are already known to be resistant to pharmacological treatment as noted above.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Limitation to the claim 13 and 15 claim language is suggested.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the

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organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.



Mark L. Berch  
Primary Examiner  
Art Unit 1624

June 25, 2003